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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,338	02/14/2001	Peter M. Glazer	YU 109 CON	9963

23579 7590 05/27/2003

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/783,338	GLAZER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED April 21, 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *21 April 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☒ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *6-14*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Jeffrey Fredman
Primary Examiner
Art Unit: 1634

Continuation of 5. does NOT place the application in condition for allowance because: Applicant requests reconsideration of the enablement rejection in view of the Glazer declaration and the late filed references. Applicant cites a variety of case law to argue that later filed references may be considered. Applicant incorrectly states that the rule is the same for showings by the Patent office and by Applicant. MPEP 2164 makes clear that while the PTO may use such later filed references to demonstrate non-enablement, Applicant may not use later filed references to demonstrate enablement. The MPEP notes " Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing". Consequently, the later art is improperly used in this case.

However, a review of all the references submitted in an untimely fashion by Applicant shows that NONE of the cited references demonstrates use of the method in vivo, as versus in cells that are in culture. In fact, the references cited by Applicant identify further problems for In vivo use of the method. For example, Vasquez et al (Nucleic Acids Res. (1999) 27(4):1176-1181) states "However, if this approach is to be of practical utility in modifying a genome, then the mutation frequency at which this occurs must be increased. (see page 1179, last sentence to page 1180)." This is an express admission that the method is not capable of function in vivo. Chan et al recognizes that the method, while perhaps a research tool in culture, is not yet ready for gene therapy, stating "Nonetheless, the TD-TFO approach as a method for DNA sequence modification has the potential to be a useful research tool and may eventually provide the basis of a gene therapy strategy. (see Chan et al, Journal of Biological Chemistry (1999) 274(17):11541-11548, see page 11548, column 2). Barre et al notes in the abstract of PNAS (2000) 97(7) that the efficiency, even in 2000, was too low for therapeutic applications in an in vitro setting, let alone an in vivo experiment.

Dr. Glazer himself, the declarant, stated in an article in Science (1996) 271 that "On the other hand, the fact that triple helix formation can lead to mutations may be an important consideration in the use of oligonucleotides in research and as therapeutics. Triplex-forming oligonucleotides designed to block transcription and even antisense oligonucleotides meant to prevent translation may have unintended and unexpected mutagenic effects." This is an express statement, by the Declarant, of the unpredictability of the invention. It is particularly striking since it is closer in time to the invention. In another paper, Dr. Glazer notes "Theoretically, targeted mutagenesis and inactivation of selected genes might also eventually have therapeutic applications. However, the general applicability of this approach will depend on the extension of the third-strand banding code and the development of nucleotide analogs so that triple helix formation is not limited to polypurine sequences. Much work in this regard is under way. Further experiments to develop a better understanding of cellular repair and replication of the triplex-directed lesion are also needed. In addition, the work reported here was performed with a highly constrained experimental model system, and targeted mutagenesis of a chromosomal gene by this approach has yet to be demonstrated. (see Mol. Cell. Biol. (1995) 15(3):1759-1768, page 1758)" This is an additional statement which indicates that undue experimentation would be required to apply the method in vivo. According to this statement, the method is not generally applicable, the work was in a highly constrained system, and no evidence that it functions on chromosomal genes exists. These statements support, and do not detract, from the enablement rejection. So to conclude the analysis of the art cited by Applicant, a final quote from a paper by Dr. Glazer regarding the goal of applying this method in vivo, "Development of novel base analogs and modifications to facilitate oligonucleotide binding, uptake, and resistance to hydrologic factors as well as research into new uses for the triplex interaction will help move this technology from the benchtop to the bedside. Clearly, however, much more work needs to be done to achieve this goal. (see Mol. Med. (1997) 75:267-282, page 282)".

So Applicant's attempt to distinguish and rely upon the prior art to enable the invention is directly rebutted by the prior art cited by Applicant, which does not support enablement of the claims.

Finally, with regard to the Declaration. The declaration relies upon both the prior art and a single experiment to support enablement of the invention. The experiment uses a particular oligonucleotide and does not support the full scope of the claimed invention, which is drawn to mutagenesis of any site in any organism. Clearly, the limited polypurine sequence drawn to a arbitrary sequence inserted into a mouse does not support enablement over the full scope of the claims. Further, even with regard to the specific example given, no evidence is provided that the amount of mutagenesis would be sufficiently significant to have any impact or use for gene therapy on the mouse. Simply correcting the mutations is not enough, the mutations must be corrected in sufficient amounts to yield some benefit or there is no patentable use for the correction method. Forming, for example, 32 mutants out of 144, 768 cells (see page 14 of declaration) would not appear to have any effect on the metabolism of the animal.

Most importantly regarding the declaration is that it is not based in the specification as filed and therefore does not show enablement of the specification at the time of filing. The declaration relies upon significant evidence which was not taught in the specification. Further, the oligonucleotides shown were not disclosed in the specification of the current claims, nor was the specific process of treatment taught by the specification.

Therefore, this Post-hoc declaration is attempting to provide enablement for an earlier filed specification by showing evidence which was not in the specification, which is not based within the specification and which is not supported by the specification. Consequently, Applicant's arguments and the Declaration are not found persuasive regarding the enablement of these claims./